Sarcopenia and Frailty in Chronic Respiratory Disease: Lessons from Gerontology

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Abstract

Sarcopenia and frailty are geriatric syndromes characterised by multi-system decline, which are related to and reflected by markers of skeletal muscle dysfunction. In older people sarcopenia and frailty have been used for risk stratification, to predict adverse outcomes, and to prompt intervention aimed at preventing decline in those at greatest risk. In this review we examine sarcopenia and frailty in the context of chronic respiratory disease, providing an overview of the common assessments tools and studies to date in the field. We contrast assessments of sarcopenia, which consider muscle mass and function, with assessments of frailty, which often additionally consider social, cognitive and psychological domains. Frailty is emerging as an important syndrome in respiratory disease, being strongly associated with poor outcome. We also unpick the relationship between sarcopenia, frailty and skeletal muscle dysfunction in chronic respiratory disease and reveal these as interlinked but distinct clinical phenotypes. Suggested areas for future work include the application of sarcopenia and frailty models to restrictive diseases and population-based samples, prospective prognostic assessments of sarcopenia and frailty in relation to common multidimensional indices, plus the investigation of exercise, nutritional and pharmacological strategies to prevent or treat sarcopenia and frailty in chronic respiratory disease.

Key words: COPD, exercise, frail, respiratory disease, rehabilitation, sarcopenia

Introduction

Skeletal muscle dysfunction is a well-recognised manifestation of chronic respiratory disease (1, 2). Among people with chronic obstructive pulmonary disease (COPD) for example, common changes in the muscular system include quadriceps weakness (3), atrophy (4), and a fibre type shift (5), each of which offers prognostic information independent of lung function (6-8). One mechanism through which skeletal muscle dysfunction may contribute to poor outcome is by precipitating so called 'geriatric syndromes'- age-related multifactorial health conditions (9) - most notably sarcopenia and frailty.

Sarcopenia describes the loss of skeletal muscle and associated decline in physical function (10), a diagnosis of which under current international consensus requires a marker of low muscle mass and reduced muscular/physical performance (11). Frailty overlaps with sarcopenia, though describes a broader syndrome characterized by vulnerability and a heightened state of risk following minor stressor events (12). Skeletal muscle dysfunction is often considered within common diagnostic criteria for frailty, via muscle weakness and a positive weight loss history that is often the product of muscle wasting (12, 13). As well as reflecting skeletal muscle dysfunction both syndromes consider wider impacts of disease, from within and beyond the lungs, which influence morbidity and mortality (14). The presence of sarcopenia or frailty can therefore be considered a 'vital sign' and provides prognostic information further to that offered by markers of skeletal muscle dysfunction alone.

In older people, sarcopenia and frailty have proved to be useful tools for risk stratification, prognostication, and to direct interventions aimed at preventing functional decline towards those carrying the greatest risk. Both are consistently associated with increased risk of

incident disability, falls, hospitalization and mortality (12, 15-20). Early intervention with exercise or nutrition can help reduce this risk, and both syndromes can be effectively managed, in some cases reversed, thus benefitting older people and their families plus reducing dependence on health and social care services. These syndromes have only recently been applied to groups with chronic respiratory disease. However, early findings have sparked interest in the field, particularly those relating to frailty which appears highly prevalent (16), a strong predictor of poor outcome (21), and provides important information for care planning, e.g. in relation to lung transplant listing (19).

In this review we consider sarcopenia and frailty syndromes in the context of chronic respiratory disease. We provide an overview of the common approaches and assessment of these syndromes from gerontology, summarize studies examining sarcopenia and frailty in people with chronic respiratory disease, and explore the relationships between these syndromes and markers of skeletal muscle weakness. Finally, we propose potential areas for future research.

Identification of literature

Studies were identified through electronic searches of Medline, EMBASE and CINAHL for articles published from January 1966 to May 2016, using key search terms based on 'sarcopenia' (muscle, sarco*, wasting), 'frailty' (frail*, geriatric) and 'respiratory disease' (COPD, fibrosis, lung disease, pulm* disease, respir*), modified according to the specific vocabulary of each database. Reference and citation lists of all identified articles were hand-searched and authors in the topic area were contacted to identify additional studies. We limited the review to studies defining sarcopenia as a syndrome, in line with an international

consensus definition, and excluded studies where sarcopenia was defined on the basis of low muscularity or low fat free mass alone (see (22) for a recent review).

Sarcopenia and frailty as Syndromes

Sarcopenia

Sarcopenia is a common condition with reported prevalence of 5–13% in those aged 60–70 years, and as high as 50% for those aged 80 or above (23). In older people sarcopenia has been associated with a number of adverse outcomes including physical disability, poor quality of life, dependency in activities of daily living and excess mortality (24, 25). The term is originally derived from the Greek words “sarx” and “penia” literally meaning “loss of flesh”, and classically sarcopenia has been defined as the “involuntary loss of muscle mass that occurs with advancing age” (26, 27). However, multiple genetic, lifestyle and environmental factors (e.g. smoking, physical inactivity, poor diet) have been shown to contribute and hasten the development of sarcopenia, irrespective of age (28, 29). With the exact aetiology of sarcopenia unknown, and knowledge of how these multiple factors interact lacking, a concrete definition of sarcopenia for use across clinical and research settings has been elusive.

More recently there has been a move to understanding sarcopenia as a clinical ‘geriatric syndrome’ rather than simply as an age-related disease. A geriatric syndrome is a term used to describe common conditions, occurring as a result of impairments across multiple physiological systems, which ultimately lead to vulnerability, poor reserve and significant morbidity and mortality (9). Geriatric syndromes do not fit typical patterns of disease, but are manifest by a number of frequently observed characteristics (9). Sarcopenia fulfils the

definition of a geriatric syndrome on a number of counts. It is without a doubt a common and complex medical condition, with multiple causative factors, and the potential for huge personal and financial cost (23). Sarcopenia is also characterised by progressive and generalised loss of skeletal muscle mass and strength, and crosses a number of diseases (24). To reflect this understanding, most consensus criteria require measurable markers of both low muscle mass and low muscle function (strength or performance) to be present for a sarcopenia diagnosis to be given (30). This view is supported by data demonstrating that loss of muscle mass does not always lead to further functional impairment (4, 31) and the relative lack of cut-points for weakness that relate to functional status (3).

Frailty

Frailty is a broader syndrome than sarcopenia that encompasses physical, social, cognitive and psychological domains. Frailty also develops as a result of multisystem age-related decline, which results in a gradual reduction in physiological reserve and increased vulnerability to sudden changes in health status which can be triggered by minor stressor events, e.g. a minor infection (12). The prevalence of frailty has been shown to increase non-linearly with adult age and is present in 10% of those over 65 years and a quarter of those older than 85 years (32). Frailty substantially increases the risk of falls, delirium, disability, institutionalisation, and death (33, 34). The prevalence of frailty is higher in women than men (35), but the relative mortality risk is lower in women than men (36).

Agreeing an operational definition for frailty has also been controversial and in the current International Classification of Diseases (ICD), frailty is listed simply as a condition of 'age-related physical disability' (ICD-10-R54). Like sarcopenia, frailty can be considered a clinical geriatric syndrome; it is common and complex, has multiple causative factors, and spans

multiple disease states. From a landmark study in older people, Fried et al. demonstrated that a combination of unintentional weight loss, exhaustion, weakened grip strength, slow walking, and low physical activity, was associated with a mortality rate of 43% at seven years in those who were frail (defined as having at least three of these characteristics), compared to only 12% among those who were not frail (35). Shortly following this work, Rockwood et al. published on a clinical Frailty Index from the Canadian Study of Health and Aging, which quantified the presence or absence of 92 variables as a ratio (37). The index suggests that frailty is a result of the proportion of deficits or diseases accumulated with age, and that this increasing deficit characterises a person's health status and determines their risk of future adverse events, including death (37, 38). An index of 0·67 (62/92 variables) identified an amount of frailty beyond which further deficit accumulation was not sustainable and death was imminent (39). This model of frailty supports Fried's concept of a reduced functional reserve, but is more explicit in the view that once a critical number of deficits have been amassed, any further insult will result in an adverse event. Here frailty can also be quantified, and the accumulated vulnerability measured, rather than dichotomised into the presence or absence of frailty as with the phenotypic models.

Contextualising sarcopenia and frailty as syndromes has helped to develop practical ways to screen, identify and assess those at high risk of adverse outcomes. By assessing contributing factors, clinicians are also able to identify appropriate strategies to reduce risk in a personalised manner, aiming to prevent or delay the occurrence of disability, falls, dependency and even death.

Assessment of sarcopenia and frailty

Sarcopenia

Numerous national and international groups have reached consensus on the definition, assessment and diagnosis of sarcopenia. There is now widespread agreement that sarcopenia should be defined as a combination of low muscle mass and loss of function, indeed a new ICD code (ICD-10-M62.84) recognizes sarcopenia as a separately reportable condition to muscle wasting or weakness alone, and age-related physical disability. Definitions typically include a measure of physical performance related to muscle loss, most often either weak hand grip strength or a slow gait speed (Table 1) (40, 41).

Consensus on measurement standards or diagnostic cut-point is still lacking. Regarding assessment of muscle mass, different groups incorporate dual x-ray absorptiometry (DXA), bioelectrical impedance analysis (BIA), and/or computational tomography assessment into their diagnostic schemes (Table 1). The ease with which these measures can be applied is variable. Whilst DXA may offer a more accurate assessment of muscle mass than BIA (42), a disadvantage is that DXA is not widely available in clinical practice, particularly within settings where sarcopenia may be particularly relevant (nursing homes or critical care). To highlight this issue, the Foundation for the National Institutes of Health (FNIH) Sarcopenia Group required measures derived from DXA and in doing so had to exclude more than half of their validation dataset in whom measures were unavailable (43, 44). In contrast, the European Working Group on Sarcopenia in Older Persons (EWGSOP) criteria are more pragmatic and accept the use of BIA, a practical measure routinely used in our day-to-day practice (45), but this may overestimate muscle mass, particularly in overweight or obese patients, resulting in a 'hidden' population with undiagnosed sarcopenic-obesity.

The assessment of physical function commonly includes an objective measure of hand grip strength and/or gait speed, both of which have strong psychometric properties assuming there is sufficient operator training and standard testing procedures to reduce measurement error (46-48). Despite consistency in the type of assessment required, important variation exists in the cut-points used. For example, cut-points for grip strength in women range from 16 to 20kg and gait speed cut-points range from 0.8 to 1.0 metres/second across the different tools (Table 1). As a result prevalence estimates for sarcopenia vary considerably, though where reported EWGSOP and FNIH criteria tend to share the highest levels of agreement (49-51).

An alternative approach to sarcopenia assessment is seen in the SARC-F, a short questionnaire designed for clinical screening. It considers falls, stair climb and lifting/carrying as functional deficits related to muscle dysfunction but does not consider markers of muscle mass. The SARC-F has been validated against three consensus definitions of sarcopenia from Europe, United States and Asia (EWGSOP, IWSOP, AWGS, see Table 1) to predict 4-year physical limitation, walking speed and chair stand (52) and could be used to identify patients in whom a more comprehensive assessment is warranted. The assessment of functional deficit in this and other sarcopenia tools underscores the overlap between sarcopenia and frailty. Gait speed and grip strength are utilised in instruments across both syndromes, especially those focusing on physical manifestations of frailty (Table 1).

Frailty

As outlined above, two predominant models of frailty have emerged; the phenotype model (35) and the cumulative deficit model (38). The phenotype model developed by Fried et al. (35) focuses on physical frailty as being distinct from disability and comorbidity. Fried's

model offers an objective measure that categorises people into three categories, frail, pre-frail and robust. An alternative, but not conflicting, perspective it that frailty is the accumulation of physiological deficits across multiple organ systems (53). Rockwood et al's Frailty Index typifies this approach by assessing frailty based on the number of deficits observed, each given equal weighting. There is flexibility in how an index is derived, as long as there are over 40 variables that fulfil specified criteria (53). This approach to frailty assessment is more inclusive than the phenotype model as it considers multiple deficits across physical, cognitive, and illness related domains that are assessed through a comprehensive assessment. In contrast to the phenotype model, disability and comorbidity are here seen as integral components of frailty, which some view as a criticism since it is contended that frailty precedes disability (38). Other common instruments such as the Edmonton Frailty Scale (54) take an even broader view of frailty and include social support within an assessment (Table 1). Sternberg and colleagues examined the most common domains within frailty instruments and identified the top three as being physical function, mobility, and cognition (55).

A recent systematic review found a total of 67 different frailty instruments, nine of which were had accumulated over 200 citations (56). Fried's phenotype was the most widely used and cited, followed by the Frailty Index from Rockwood et al (38). Other common instruments include the Clinical Frailty Scale and the FRAIL scale, the use of which has increased dramatically in the last decade (56, 57). Frailty instruments vary widely in terms of the domains assessed, whether objective tests are included, and data sources. For instance, the FRAIL scale uses five self-report questions, whereas the Edmonton Scale (54) requires a drug review, tests of cognitive and physical function, plus assessments of Activities of Daily

Living (ADL) dependence, mood and general health. Frailty may be assessed in clinical practice, research, or in policy (56). Each instrument has its advantages and disadvantages (58) and the choice of an instrument should reflect the context and overall purpose of assessment. In clinical practice frailty assessment may guide decision-making around an approach to care, decision to undertake an investigation or procedure, or signposting to other services. A nurse may consider the FRAIL scale to screen for frailty due to its ease and simplicity, or turn to the more holistic Edmonton Scale, which although more time consuming to complete may help them understand what is causing someone's frailty to direct input from other services. In research frailty instruments have mostly been used to predict adverse outcome (56), but their role to determine eligibility for a study, or as a target for intervention should not be overlooked. In the case of a physical exercise intervention Fried's model is well suited given its focus on physical frailty (20) whereas for more integrated approaches an global instrument from frailty may be more appropriate.

Sarcopenia and Frailty in Chronic Respiratory Disease

There are limited studies examining sarcopenia and frailty in chronic respiratory disease to date and a reliance on the stable disease setting, which is important to recognize given that exacerbations and/or hospitalisation will hasten deconditioning and likely increase sarcopenia and frailty states (1, 2). Only one study has focused on sarcopenia (59), which found a 15% prevalence in people living with stable COPD (Table 2). Of those studies examining frailty prevalence, the overall interpretation is that frailty is increased in the presence of chronic respiratory disease. Only a single retrospective study suggested frailty is not increased in respiratory disease and this concerned patients with very mild disease (mean (SD) FEV_1 79.6 (25.2) % predicted)(17). Prevalence estimates vary considerably across

the studies, ranging from 5-65% for frailty and 22-64% for pre-frailty (Table 2). This variation is likely due to differences in both the criteria used and populations or settings studied. Frailty prevalence has been associated with a number of factors including physical inactivity, impairment due to breathlessness, poor respiratory function, and increasing comorbidity burden (17, 20, 21). When assessed cross-sectionally the combination of frailty and these factors has led to poorest outcomes, with evidence of a cumulative adverse effect (17, 60).

Consistent with the literature in older people, studies demonstrate that frailty is associated with poor outcomes in chronic respiratory disease including increased falls, hospitalizations, and greater levels of disability (16, 19, 59, 61). Prospective studies also support frailty as a predictor of mortality; often being frail at least doubles the risk of mortality, which has obvious implications for effective disease management (17, 60, 62) (Table 2). There are also examples of frailty adversely affecting patients' odds of receiving disease modifying surgical (19) and non-pharmacological (20) treatments, which should equally be considered an important adverse outcome.

Pulmonary rehabilitation has been shown to improve outcomes in both sarcopenic and frail patients. Improvements in symptom burden, physical function and overall health status have been demonstrated following a rehabilitation programme, and in some patients this led to a reversal and declassification of their sarcopenia and frailty status (20, 59, 61). The change in status partly reflects the working of phenotype models, as patients falling close to one or more cut-points only require a small improvement for their status to be changed. Nonetheless there is significant overlap between key characteristics of sarcopenia and frailty and common targets of rehabilitation, e.g. muscular strength, physical activity and vitality. The presence of sarcopenia does not appear to restrict patients from participating in

pulmonary rehabilitation (59), but the impairment associated with frailty does seem to hinder completion of a programme. Of those referred for rehabilitation in one study, being frail doubled a patient's odds of programme non-completion (20).Although limited to one study, there is some evidence to suggest that the relationship between frailty and chronic respiratory disease could be bi-directional. Vaz Fragoso et al. observed that frailty was associated with increased odds of developing respiratory impairment, and conversely respiratory impairment was associated with increased odds of developing frailty (60). This finding needs to be confirmed, and perhaps extended to exacerbations of disease where respiratory impairment can persist (63), but could have important implications as strategies targeting one condition may be extend to both.

Another interesting aspect linking frailty and chronic respiratory disease warranting further study is the role of inflammatory biomarkers (19). It is possible that cachectic COPD patients with persistent inflammation could be at particular risk for the development of frailty, and it is therefore important to better understand this potentially treatable biological mechanism.

Relationships between skeletal muscle weakness, sarcopenia and frailty

Two cohort studies arising from the Harefield Hospital Pulmonary Rehabilitation service (20, 59) provide data to examine the relationships between skeletal muscle weakness, sarcopenia and frailty in more detail (see Table 2). Of 90 participants with COPD who were sarcopenic by EWGSOP criteria, 89% had hand grip weakness, 54% a slow gait speed, and 48% both markers of reduced physical performance. An additional 27 participants from this study (4% of the overall sample) had low skeletal muscle index without either marker of reduced physical performance. In this sub-group group there was also no evidence of reduced global function or exercise capacity. This supports the contemporary view of

sarcopenia requiring a degree of functional muscular impairment in that adding low physical performance to a sarcopenia diagnosis appears to further differentiate those with and without the syndrome. In a related but larger cohort, 209 participants were found to be frail by Fried's phenotype criteria. Among this frail group the majority of patients demonstrated hand grip weakness (80%) and had a slow gait speed (72%) (20). These findings endorse the view that muscle dysfunction is an important contributor to sarcopenia and frailty in chronic respiratory disease.

Another way to explore muscle dysfunction in relation to sarcopenia and frailty is to observe upper and lower limb muscle strength according to the presence of these syndromes. Mean (SD) hand grip strength values of 21.5 (7.5) kg and 21.3 (8.2) kg were found among sarcopenic and frail patients from the two studies respectively, compared with values of 27.6 (10.0) and 33.0 (8.9) kg among other study participants. Whilst these values are in part a product of the diagnosis for sarcopenia or frailty, values for the lower limb (which are note considered in a diagnosis) revealed a similar pattern. Quadriceps maximum voluntary contraction values of 19.8 (7.6) kg and 21.0 (9.0) kg were found among sarcopenic and frail patients respectively, compared with 27.1 (10.2) kg and 31.0 (10.1) kg among those not sarcopenic or not frail in the two studies. The between groups differences of about 8-10kg are likely to be clinically significant but this needs to be confirmed. The ratios of upper:lower limb strength are also noteworthy, with mean hand grip values exceeding those for the quadriceps, which reflects the propensity of muscle dysfunction in COPD towards the lower limbs (1, 2).

The relationships between sarcopenia, frailty and quadriceps weakness, defined according to healthy predicted values (64),could be further explored in 707 participants with full

measurements. A complex interplay exists between quadriceps weakness, sarcopenia and frailty, which appear as overlapping but distinct clinical phenotypes (Figure 1). With the caveat that each phenotype depends on cut-points used (derived from observational studies), quadriceps weakness was the most common phenotype, observed in 57% of patients, followed by frailty, observed in 23%, and sarcopenia, observed in 12%. About two-thirds (64%) of those patients with quadriceps weakness did not exhibit concurrent sarcopenia or frailty, whereas only a minority of patients with frailty (16%) had neither quadriceps weakness nor sarcopenia. Just 3% of patients had all three phenotypes and we hypothesise this group carry the highest risk of adverse outcome (Figure 1).

Future directions and opportunities

Having reviewed current evidence around sarcopenia and frailty in chronic respiratory disease, future work may include; applying models to groups not represented in studies to date, e.g. restrictive diseases; comparing the prognostic utility of sarcopenia and frailty models against each other and multidimensional indices; optimising exercise-based treatments to manage these syndromes; and exploring additional strategies focused on nutrition, lifestyle factors, and pharmaceuticals.

The evidence to date is biased towards studies of frailty rather than sarcopenia, phenotypic rather than cumulative deficit models of frailty, COPD rather than other chronic lung diseases, and stable rather than acute settings. Applying sarcopenia and frailty models across the range of diseases and settings will be necessary to fully understand these syndromes and their value to the field. Recent studies have assessed constructs closely related to sarcopenia and frailty in the acute setting, e.g. localised muscle wasting (65) and gait speed (18), and provide a strong basis on which examine validated models of

sarcopenia and frailty. Studies investigating the prognostic utility of sarcopenia and frailty have generally been retrospective and used modified frailty criteria that deviated from validated instruments. Again, new prospective validations based on this work should be undertaken to confirm these initial findings, adhering to the original instruments, and capturing outcomes using robust collection methods. Further, as studies have made use of existing datasets, the adverse outcomes collected are often limited to mortality alone, and the full range of outcomes common to geriatric syndromes has not been exploited. As well as tracking mortality studies should, where possible, assess incident falls, ADL disability, care home admission and hospitalisation. The comparative prognostic value of these syndromes, both in relation to each other and to leading prognostic indices, e.g. ADO and BODE, should also be tested if they are to compete as mainstream clinical markers.

Future work should also address how sarcopenia and frailty can be optimally managed within respiratory disease. Exercise-based strategies can be used to reduce the impact of these syndromes on patients and the evidence suggests both and frailty can be reversed not just prevented, a notion supported by the gerontology literature (66). The holistic pulmonary rehabilitation model has proven to be highly effective at improving health status in respiratory disease. Many components of this model target sarcopenia and frailty related outcomes, e.g. falls prevention strategies. The ‘dose’ of rehabilitation delivered through the model also appears sufficient to change sarcopenia and frailty domains, which suggests a reduced risk of adverse events occurring, though this needs to be confirmed. Given the difficulty frail people experience completing a programme, further work is required to understand how better to support frail patients, perhaps via organisational changes, e.g. transport schemes or flexible class scheduling (67), or via supplementary training strategies,

e.g. muscle stimulation (68). The overarching goal would be for more people to access and benefit from a rehabilitation approach.

Additional treatment strategies could include nutritional interventions and review of polypharmacy. Nutritional assessment should be an integral part of holistic disease management, but is often overlooked or not given sufficient attention (22). In some patients malnutrition may be a key driver of the sarcopenia and frailty syndromes and appropriate nutritional support may be paramount to bringing meaningful change. Finally, with increasing multi-morbidity more patients are prescribed multiple medicines. The introduction of a new drug can represents a stressor and the cumulative side effects and/or drug interactions can contribute directly to frailty (12). Tools to support evidence-based medication reviews and/or appropriate rationing are advocated for the care of older people (15, 69, 70). Conversely, the advent of medicines directed specifically at muscle (71) may change the treatment landscape and offer new prospects in sarcopenia and frailty management in chronic respiratory disease and beyond.

Summary

Sarcopenia and frailty are geriatric syndrome that are related to and reflected by markers of skeletal muscle dysfunction. Numerous instruments have been validated to help assess sarcopenia and frailty, and the choice of one over another depends on the context and primary purpose of assessment. Both sarcopenia and frailty are common in people with chronic respiratory disease and prevalence is positively associated with increasing age, disease severity, symptom and comorbidity burden. Frailty assessment can be used to

identify patients with chronic respiratory disease at increased risk of falls, hospitalizations, and mortality, in whom preventative interventions can be commenced. A complex interplay exists between quadriceps weakness, sarcopenia and frailty, which are overlapping but distinct clinical phenotypes. Suggested areas for future work include studies in the acute setting, the prospective prognostic assessment of sarcopenia and frailty models in relation to each other and to current multidimensional indices, as well as the continued investigation of exercise, nutritional and pharmacological strategies to help prevent or treat sarcopenia and frailty in chronic respiratory disease.

Table 1: Assessment domains of common sarcopenia and frailty instruments

	Domains													
	Muscle mass	Physical performance/ mobility	Muscle strength	Physical activity	Falls	Exhaustion/ fatigue	Weight loss	General health	Physical symptoms	Functional independence	Cognition	Social support	Psychological symptoms/ Mood	Medication use
Sarcopenia														
Society for Sarcopenia, Cachexia and Wasting Disorders, Sarcopenia with limited mobility(15)	Appendicular lean mass index (>2 SD below mean)	6MWT (<400m) or Gait speed (<1.0m/s)	-	-	-	-	-	-	-	-	-	-	-	-
European Society for Clinical Nutrition and Metabolism (ESPEN) (72)	Muscle mass (>2 SD below mean)	4MGS (<0.8m/s)	-	-	-	-	-	-	-	-	-	-	-	-
European Working Group on Sarcopenia in Older Persons (EWGSOP)(73)	BIA skeletal muscle index (men <8.5 kg/$m^{2;}$ women <5.75kg/m^2)	4MGS (<0.8m/s)	Grip strength (men <30kg, women <20kg)	-	-	-	-	-	-	-	-	-	-	-
International Working Group Sarcopenia (IWGS) Task Force(74)	Appendicular lean mass index (men <7.23 kg/m^2 women <5.67 kg/m^2)	4MGS (<1.0 m/s)	-	-	-	-	-	-		-	-	-	-	-

Asian Working group for Sarcopenia (AWGS) (75, 76)	DXA (men 7.0 kg/m2 women 5.4 kg/m2) Or BIA (men 7.0 kg/m2 women 5.7 kg/m2)	6MGS (≤0.8m/s)	Grip strength (men <26kg women <18kg)	-	-	-	-	-	-	-	-	-	-	-
Foundation for the National Institutes of Health (FNIH) Sarcopenia Project (49)	DXA appendicular lean mass/ BMI (men 0.512 women 0.789)	4/ 6 MGS (<0.8m/s)	Grip strength (men <26kg women <16kg)	-	-	-	-	-	-	-	-	-	-	-
SARC-F (52)	-	Assistance walking across a room	Difficulty lifting and carrying 10lb, difficulty climbing 10 stairs	-	Falls (past year)	-	-	-	-	Transfer from chair or bed	-	-	-	-
Frailty														
Fried's Frailty Phenotype(35)	-	4MGS	Grip strength	Physical activity level	-	Self-reported exhaustion	Weight loss (≥5% in last year)	-	-	-	-	-	-	-
FRAIL Scale (57)	-	Ability to walk several hundred yards	Ability to climb a flight of stairs	-	-	Tiredness	Weight loss (≥5% in last 6 month)	Illnesses (≥5)	-	-	-	-	-	-
CSHA Clinical Frailty Scale(38)	-	Mobility	-	Physical activity level	-	Tiredness	-	-	Level of active symptoms	Help with ADLs	Dementia	-	-	-
Frailty Index (77) (defined	-	Mobility,	-	-	Falls	Tiredness	-	Illnesses	-	Help with	Memory,	Social	Mood	-

according to 70 deficits (38))		gait pattern								ADLs	cognition	support		
E-Frailty Index (78) (defined according to 36 deficits)	-	Mobility, transfers	-	Activity limitation	Falls	-	Weight loss, anorexia	Presence of chronic conditions	Symptoms including dyspnoea, dizziness	Care Require-ment	Memory, cognition	Social support, house-bound	-	≥5 drugs prescribed
Tilburg Frailty Indicator(79)	-	Walking	Strength in hands	Physical activity level	-	Tiredness (physical)	Weight loss	Physical health	Balance, vision and hearing		Cognition	Social support, relations, living status	Depression, anxiety, coping	
Edmonton Scale (54)	-	Timed up and go test	-	-	-	-	Weight loss (yes/ no)	General health	-	Help with ADLs, continence	Draw clock-face task	Social support	Sadness, depression	≥5 drugs prescribed

Legend: 6MWT = 6 minute walk time; 4MGS = 4 metre gait speed; DXA= dual x-ray absorptiometry; BIA= bioelectrical impedance analysis; ADLs= activities of daily living

Table 2. Studies of sarcopenia and frailty syndromes in chronic respiratory disease

Reference	Design	Sample	Key measures	Main findings	Implications
Sarcopenia					
Jones et al. 2015 (59)	Cross-sectional Case-control	622 with COPD 43 sarcopenic patients and 43 propensity score-matched controls pre-post rehabilitation	EWGSOP criteria ISWT QMVC CAT Physical activity by questionnaire and accelerometry	Overall prevalence of sarcopenia 15%. Prevalence associated with age, breathlessness and disease severity. Sarcopenic patients had reduced exercise capacity, functional performance, physical activity and health status ($p<0.001$). Outcomes to pulmonary rehabilitation were similar across patients with sarcopenia and a propensity matched control group. Following rehabilitation 12/43 (28%) sarcopenic patients no longer met EWGSOP criteria.	Sarcopenia is a distinct phenotype from generalised muscle wasting or physical function alone, and is associated with a worse functional and health status. Response to pulmonary rehabilitation is not impaired by sarcopenia and can lead to a reversal of the syndrome in some patients.
Frailty					
Akgün et al. 2016 (80)	Prospective cohort	7144 (3538 HIV positive) of whom: 154 HIV positive with COPD 182 HIV negative without COPD	4-item adapted of Fried's Frailty Phenotype Physical Limitation Scale	Prevalence of frailty in patients with COPD 59% and 58% in those with HIV positive and negative status respectively. COPD was associated with increased odds of being frail ($p<0.01$) and with physical limitation ($p<0.001$). COPD associated with 5-fold greater odds of frailty in HIV positive group, and 3.5 fold grater odds in those with HIV negative status.	Optimizing COPD management may be important to minimize frailty and maintain physical function for individuals aging with HIV.
Valenza et al. 2016 (81)	Cross-sectional	212 with COPD (104 stable, 108 acute during exacerbation) 100 without COPD	Fried Frailty Phenotype Physical activity questionnaire Barthel Index Charlson Index	Prevalence of frailty 63% in acute COPD and 65% in stable COPD. Cut-points to detect frailty using Baecke questionnaire 3.54 and 3.88 for acute and stable COPD.	Measuring physical activity can help to predict the presence of frailty in acute and stable COPD. Interventions aimed at increasing physical activity may reduce or delay frailty.

Park et al. 2013 (21)	Cross-sectional	98 chronic bronchitis 70 COPD 43 chronic bronchitis & COPD	9 item criteria of frailty (based on Tilburg Frailty Indicator) Physical activity by accelerometry Basic and instrumental ADLs	Prevalence of frailty 58% and of pre-frailty 22%. Self-reported breathlessness was the strongest predictor for frailty (odds ratio 3.98 95% CI 1.79-8.88, p<0.05). Frail patients had a greater number of disabilities and poorer outcomes including difficulties in ADLs.	Highlights the importance of recognising Frailty is highly prevalent in COPD and may have implications for care. Knowledge of frailty determinants can help health care providers identify pre-frail patients and provide preventative interventions to delay frailty onset.
Mittal et al. 2016 (16)	Prospective cohort	120 Chronic pulmonary disease (67 COPD)	Fried Frailty Phenotype Physical activity questionnaire 100 foot walk test	Prevalence of frailty 18% and pre-frailty 64%. Frailty was associated with increased number of falls (p=0.018) and hospitalizations (p=0.011) in past year. Gait speed correlated with frailty status (r^2=0.36, p<0.001) and decreased as frailty increased (p=0.001).	Frailty could help predict falls and frail patients may benefit from a comprehensive geriatric assessment. Gait speed may help screen for frailty in chronic respiratory disease, but is only a single component of frailty.
Galizia et al. 2010 (62)	Cross-sectional with mortality follow up	489 with COPD 799 without COPD	Frailty Staging System Basic ADLs Charlson Index	Prevalence of frailty 49%. With increasing frailty stage, mortality at follow up (12 years) increased from 54% to 97% in patients with COPD (p<0.001).	Clinical frailty stage offers prognostic information on long term mortality risk in people with COPD.
Lahousse et al. 2015 (17)	Prospective cohort	402 with COPD 1,740 without COPD	Fried Frailty Phenotype Spirometry Exacerbation history	Prevalence of frailty 5% and pre-frailty 45% Those with COPD more than twice as likely to be frail (odds ratio 2.2, 95% CI 1.34-3.54, p=0.002). Prevalence of frailty in COPD associated with breathlessness, airflow limitation, and frequent exacerbations. Frailty was an important determinant of mortality in COPD (hazard ratio 4.03, 95% CI 1.22-13.30, p=0.022) along with lung function and comorbidity count.	Increased prevalence of frailty with COPD related to breathlessness and exacerbation frequency. For patients with COPD, frailty appears to offer prognostic information on mortality risk.
Vaz Fragoso et al. 2012 (60)	Prospective cohort	3578 older persons (262 with COPD)	Fried Frailty Phenotype Spirometry 15 foot walk test	Prevalence of frailty in patients with COPD 10% and pre-frailty 54%.	Frailty and respiratory impairment increase mortality risk, especially when both are present.

				Frailty associated with increased airflow limitation (odds ratio 1.88, 95% CI 1.15 to 3.09), and restrictive lung function (odds ratio 3.05, 95% CI 1.91 to 4.88). In those without respiratory impairment at baseline, frailty was associated with increased odds of developing respiratory impairment at 4 years (odds ratio 1.42, 95% CI 1.11 to 1.82). In those not frail at baseline, those with respiratory impairment had increased odds of developing frailty at 3 years (odds ratio 1.58, 95% CI 1.17 to 2.13). Greater mortality in those with frailty and respiratory impairment (2.5 fold increase in those with both compared to neither) during follow up.	There may be a bidirectional relationship between frailty and respiratory impairment which could be important for therapy. Strategies targeting frailty- or respiratory-related impairment may extend to both conditions.
Singer et al. 2015 (19)	Prospective cohort	395 Lung transplant candidates	Fried Frailty Phenotype SPPB 6MWD Blood Biomarkers (IL-6, TNFR1, IGF-1, leptin)	Prevalence of frailty based on Fried Frailty Phenotype 28%. Prevalence was not associated with low skeletal muscle index. Frailty was associated with higher levels of plasma IL-6 and TNFR1, and lower levels of IGF-1 and leptin. Frailty was associated with greater disability and twice the incidence of delisting or death before transplantation (27% vs. 13%, p=0.077).	Frailty assessment could provide important morbidity and mortality risk information. Frailty assessment could be used to identify lung transplant candidates at increased risk of post-transplant disability or poorer outcomes.
Mittal et al. 2015 (61)	Prospective cohort	30 Chronic pulmonary disease (23 COPD)	Fried Frailty Phenotype Physical activity questionnaire 100 foot walk test	Prevalence of frailty 17% and pre-frailty 61%. Patients with frailty had frequent falls and hospitalisations within the last year. Following pulmonary rehabilitation, gait speed was improved (mean 0.88 to 1.02 m/s, $p<0.001$) and 3/5 (60%) previously frail patients were no longer met case criteria for frailty.	Pulmonary rehabilitation may improve frailty specifically through an effect on gait speed in some patients, but this effect is not consistent.
Maddocks et al. 2016 (20)	Prospective cohort	816 COPD	Fried Frailty Phenotype MRC dyspnoea score Physical activity questionnaire	Prevalence of frailty 26% and pre-frailty 64%. Prevalence of frailty increased with age, GOLD stage, MRC score and comorbidity burden	Frailty is an independent predictor for pulmonary rehabilitation non-completion.

			ISWT HADS CRQ CAT	(p<0.001) Frailty associated with over twice the odds of pulmonary rehabilitation non-completion (odds ratio 2.20, 95% CI 1.39-3.46, p=0.001). Patients who were frail had better treatment outcomes following rehabilitation, including better responses in MRC score, exercise capacity, physical activity and health status (p<0.001). 71/115 (62%) previously frail patients no longer met case criteria for frailty following pulmonary rehabilitation.	This highlights the importance of understanding frailty in the management of COPD and should prompt exploration of new ways to support frail patients through rehabilitation.

Legend: ADLs=Activities of Daily Living; CAT=COPD Assessment Test; CRQ=Chronic Respiratory Questionnaire; EWGSOP=European Working Group on Sarcopenia in Older People; GOLD=Global Initiative for Chronic Obstructive Lung Disease; HADS=Hospital Anxiety and Depression Scale; IGF-1=Insulin-like Growth Factor 1; IL-6=Interleukin 6; ISWT=Incremental Shuttle Walk Test; QMVC=Quadriceps Maximum Voluntary Contraction; SPPB=Short Physical Performance Battery; TNFR1=Tumor Necrosis Factor Receptor 1; 6MWD=6 Minute Walk Distance

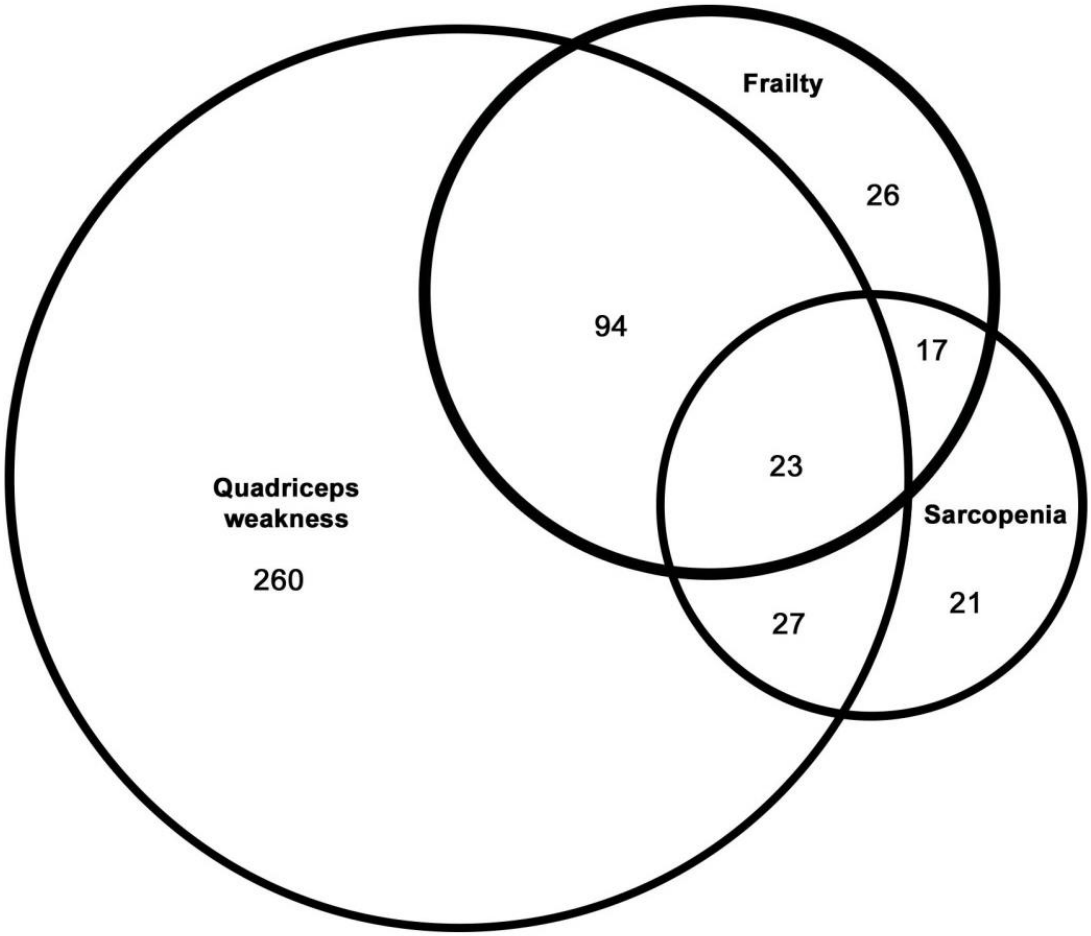

Figure 1. Relationships between frailty, sarcopenia and quadriceps weakness in patients with COPD derived from (20). Numbers represent patients with each phenotype (n=707).

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